Changes in muscle strength, relaxation rate and fatiguability during the human menstrual cycle

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1. The effect of the different phases of the menstrual cycle on skeletal muscle strength, contractile properties and fatiguability was investigated in ten young, healthy females. Results were compared with a similar group on the combined (non-phasic) oral contraceptive pill (OC). Cycle phases were divided into the early and mid-follicular, mid-cycle (ovulatory) and mid- and late luteal. Cycle phases were estimated from the first day of the menstrual bleed.

2. Subjects were studied weekly through two complete cycles. Measurements included quadriceps and handgrip maximum voluntary isometric force and the relaxation times, force–frequency relationship and fatigue index of the quadriceps during percutaneous stimulation at a range of frequencies from 1 to 100 Hz.

3. In the women not taking the OC there was a significant increase of about 11% in quadriceps and handgrip strength at mid-cycle compared with both the follicular and luteal phases. Accompanying the increases in strength there was a significant slowing of relaxation and increase in fatiguability at mid-cycle. No changes in any parameter were found in the women taking the OC.

4. The changes in muscle function at mid-cycle may be due to the increase in oestrogen that occurs prior to ovulation.

Recent work has suggested that oestrogen can influence the force generating capacity of skeletal muscle. Initial evidence for such an effect came from cross-sectional studies on pre- and post-menopausal women. Muscle becomes weaker following the menopause because of both a reduction in muscle size and a decline in force generating capacity (i.e. force per unit cross-sectional area (CSA)). This has been demonstrated for the adductor pollicis (AP) (Phillips, Rook, Siddle, Bruce & Woledge, 1993*b*) and quadriceps (Rutherford & Jones, 1992) muscles. The reduction in force per unit CSA can be prevented in the AP by hormone replacement therapy (HRT) (Phillips *et al.* 1993*b*) suggesting that the decline in sex hormone levels following the menopause is affecting the ability of the muscle to generate force. To investigate this further Phillips, Gopinathan, Meehan, Bruce & Woledge (1993*a*) measured the isometric strength of the AP during the menstrual cycle and found that there was a peak in strength around the time of ovulation. One of the major hormonal changes to occur following the menopause is a decrease in oestrogen whilst, conversely, there is a peak in oestrogen prior to ovulation during a normal menstrual cycle. Together these results pointed to a fairly rapid effect of oestrogen on skeletal muscle force production.

Previous studies of muscular performance during the menstrual cycle have concentrated mainly on changes in endurance performance, rather than strength, and have usually compared the early follicular and luteal phases (for review see Lebrun, 1994). Those studies which have looked at explosive power events have mainly measured performance levels, which are influenced by many variables other than muscle strength or power output. One study investigated the changes in handgrip strength and standing long jump during the menstrual, ovulatory and luteal phases of the cycle (Davies, Elfors & Jamieson, 1991). The only significant difference found was a stronger handgrip strength during the menstrual phase, which the authors attributed to the lower oestrogen and progesterone levels. These results therefore conflict with those of Phillips *et al.* (1993*a*).

Despite the high level of interest in the effect of the menstrual cycle on athletic performance and fitness, there remains considerable controversy in the literature. The purpose of this study was to investigate the effect of the menstrual cycle phase on simple tests of muscle strength in large muscle groups which are important in many sporting and everyday tasks (quadriceps and handgrip). In order to

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test more rigorously any effect of female sex hormones on muscle, the stimulated contractile properties of the quadriceps muscle were also measured. These have the advantage of being objective and independent of motivation. A group of women taking the oral contraceptive pill were chosen as 'controls' because oestrogen levels remain fairly constant for the 21 days of administration.

Preliminary reports of this work have been published (Sarwar, Beltran Niclos & Rutherford, 1995; Phillips, Rutherford, Birch, Bruce & Woledge, 1995).

METHODS

Subjects

Two groups of ten young, healthy, relatively sedentary women were recruited and studied through two complete cycles. The first group of women were not taking any form of hormonal treatment (age, 20·7 ± 1·4 years; height, 1·65 ± 0·67 m; weight, 57·8 ± 10·6 kg; means ± S.D.) and all had regular cycles lasting between 26 and 32 days (mean, 28). The second group had been taking a combined oral contraceptive pill (OC) for at least 6 months (age, 20·5 ± 1·1 years; height, 1·63 ± 0·44 m; weight, 56·6 ± 4·6 kg). All the women in the OC group were taking a combined (non-phasic) pill with low-dose ethinyl oestradiol (20–35 μg) together with progestins in different doses. All the subjects gave their written informed consent and the study was approved by the Parkside Ethical Committee.

Protocol

All the women were tested weekly through two complete cycles and results are reported for the cycle in which measurements coincided with the phases described below. On each occasion both legs were tested and the mean for the two legs is reported. Cycle phases were estimated back from the first day of bleeding (day 1) with ovulation being predicted as 14 days prior to menstruation. This method was chosen because the luteal phase is usually more constant in length than the follicular phase. Cycle phases are termed: early follicular (EF, between days 1–7); mid-follicular (MF, between days 7–12); mid-cycle (MC, between days 12–18); mid-luteal (ML, between days 18–21); and late luteal (LL, days 21–32).

Quadriceps strength

The maximum voluntary isometric strength (MVC) of the quadriceps was measured using a conventional strength testing chair similar to that described by Edwards, Young, Hosking & Jones (1977). The best of three MVCs was measured at each test and the results expressed in newtons (N). During the manoeuvre a percutaneous twitch superimposition technique was used to test whether subjects could maximally activate their quadriceps during the isometric contraction (Rutherford, Jones & Newham, 1986).

Contractile properties

The contractile properties of the quadriceps muscle were measured using stimulated contractions. With the subject seated in the strength testing chair as described above, two large flexible rubber electrodes were placed over the muscle. Percutaneous electrical stimulation with unidirectional square-wave pulses of 200 μs duration and 400 V were applied via a Digitimer stimulator (Type D37) triggered by a Digitimer programmer (Type D4030). With the stimulation frequency set at 40 Hz, current strength was adjusted so that between 20 and 30% of the muscle was stimulated. Following a 2 min rest period, the muscle was then stimulated for 3 s at 1, 10, 20, 50 and 100 Hz with a rest period of about 30 s between each. The forces generated at each frequency were expressed as a percentage of the force generated at 100 Hz.

The half-time of relaxation from the twitch was calculated as the time for the muscle to relax from peak to half-peak force ($t_{½}$). To minimize the effects of fatigue and potentiation, a standardized procedure was adopted in which the twitch was measured 1 min after the MVC and before any other measurements were carried out. Relaxation times from a tetanus were calculated from the 50 Hz (T_{50}) and 100 Hz (T_{100}) contractions as the time taken for the force to drop from three-quarters to three-eighths of maximum. On some testing occasions, the measurement of $t_{½}$, T_{50} and T_{100} was not possible because the muscle did not relax smoothly; superimposed on the relaxation there was a secondary, lower contraction. This may have been caused by stimulation of afferent fibres resulting in an H-reflex or, more likely, antidromic stimulation of the motor efferents causing an F wave.

Fatiguability

An adapted Burke protocol (Burke, Levine, Tsairis & Zajac, 1973) was used to measure the fatiguability of the quadriceps. The muscle was stimulated at 40 Hz for 0·25 s every second for 3 min. The fatigue index (FI) was measured as the percentage force lost over the 3 min. The C.V. of the FI was $<10\%$ when care was taken to stimulate the same percentage of the muscle on each testing occasion.

Handgrip strength

Grip strength was measured using a Jamar hydraulic hand dynamometer (JA Preston, Jackson, MI, USA). The handle was adjusted according to hand size and the manoeuvre was carried out with the arm by the side of the body and the elbow extended. Again, the best of three attempts was recorded.

Statistics

Differences between cycle phases were compared using ANOVA and differences identified were then tested using Student's paired t test. Student's unpaired t test was used to test differences between the two groups. Data are presented as means ± S.E.M. for each group ($n = 10$).

RESULTS

Quadriceps strength

Quadriceps strength peaked during MC in the non-pill group. There were significant differences in the MVC between MC and all other phases of the cycle (EF, $P < 0·001$; MF, $P < 0·01$; ML, $P < 0·005$; LL, $P < 0·001$), with the greatest difference being between MC and LL phases (11·7% ± 5·3; mean ± S.D.). There were no significant differences in the MVC between phases for the women taking the OC. The results for both groups are shown in Fig. 1*A*. The OC group tended to be weaker than the non-pill group which was probably because of the lower mean body weight of the OC group. The difference was only significant during the MC phase ($P < 0·05$). All the women could fully activate the quadriceps on each testing occasion.

Handgrip strength

The grip strength was also significantly greater at MC compared with all other phases (for all phases $P < 0·001$).

Table 1. Force–frequency relationship for the non-pill group at MC and ML phases

Cycle phase	1/100 (%)	10/100 (%)	20/100 (%)	50/100 (%)
Mid-cycle (MC)	25·0 ± 1·8	50·5 ± 2·2	76·7 ± 1·1	95·8 ± 0·5
Mid-luteal (ML)	21·5 ± 1·4	47·0 ± 1·5	70·9 ± 1·1 *	89·6 ± 0·9 **

Data expressed as means ± S.E.M. Significant difference between phases, Student's paired t test: * $P < 0·005$, ** $P < 0·001$.

Once again the greatest differences were seen between MC and luteal phases (ML 11·5% ± 6·1; LL 11·1% ± 7·0). There were no significant differences between any of the phases for women taking the OC (Fig. 1*B*). The handgrip strength was lower in the women taking the OC compared with the non-pill group. The differences were significant between the groups for phases EF, MF and MC.

Quadriceps contractile properties

The relaxation time from a twitch ($t_{½}$) was slowest at MC. There were significant differences between MC and EF, ML and LL (EF, $P = 0·005$; ML, $P < 0·001$; LL, $P < 0·001$). No differences in $t_{½}$ between phases were found for the OC group (Fig. 2*A*).

The relaxation times from tetani (T_{50} and T_{100}) were also slowest during MC compared with other phases. For T_{50} the differences were significant for all phases apart from MF (EF, $P < 0·01$; ML, $P < 0·005$; LL, $P < 0·001$; Fig. 2*B*). For T_{100} the differences were not significant between MC and the follicular phases but were for the luteal phases (ML, $P < 0·02$; LL, $P < 0·001$).

As the muscle became slower during MC in the non-pill group, there was a corresponding leftward shift in the force–frequency relationship (Table 1). The difference in the forces (as a percentage of that at 100 Hz) was significant for the 20/100% at ML ($P < 0·05$) and for 50/100% at all phases (EF, $P < 0·005$; MF, $P < 0·05$; ML, $P < 0·001$;

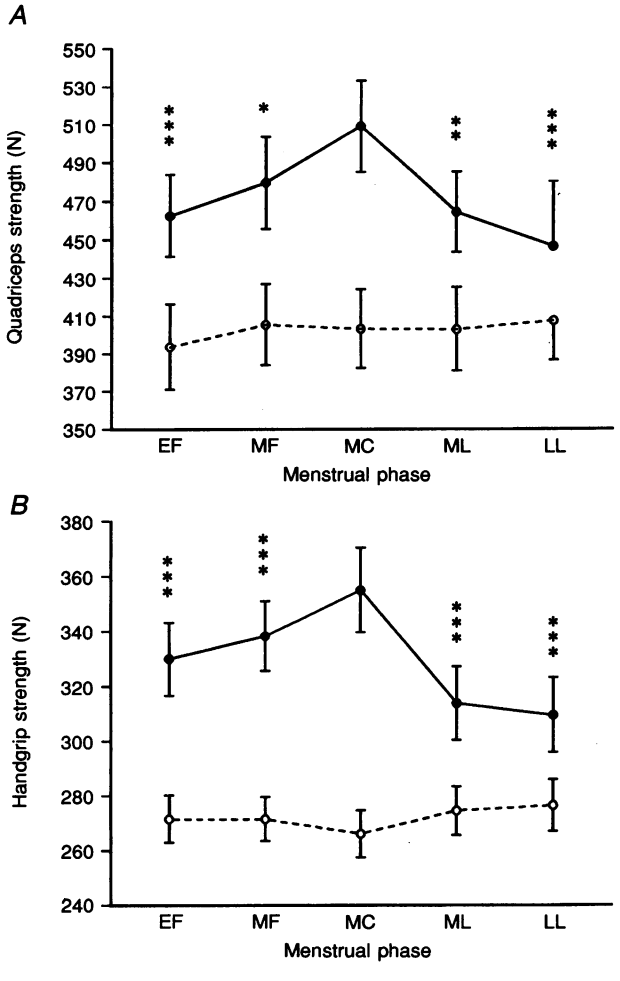

Figure 1. Mean quadriceps and handgrip strength at different phases of the cycle

Quadriceps (*A*) and handgrip (*B*) strength for the non-pill (●) and OC (○) groups at different phases of the cycle: EF, early follicular; MF, mid-follicular; MC, mid-cycle; ML, mid-luteal; LL, late luteal. Significant difference from MC: * $P < 0·01$, ** $P < 0·005$, *** $P < 0·001$. Data shown as means ± S.E.M.

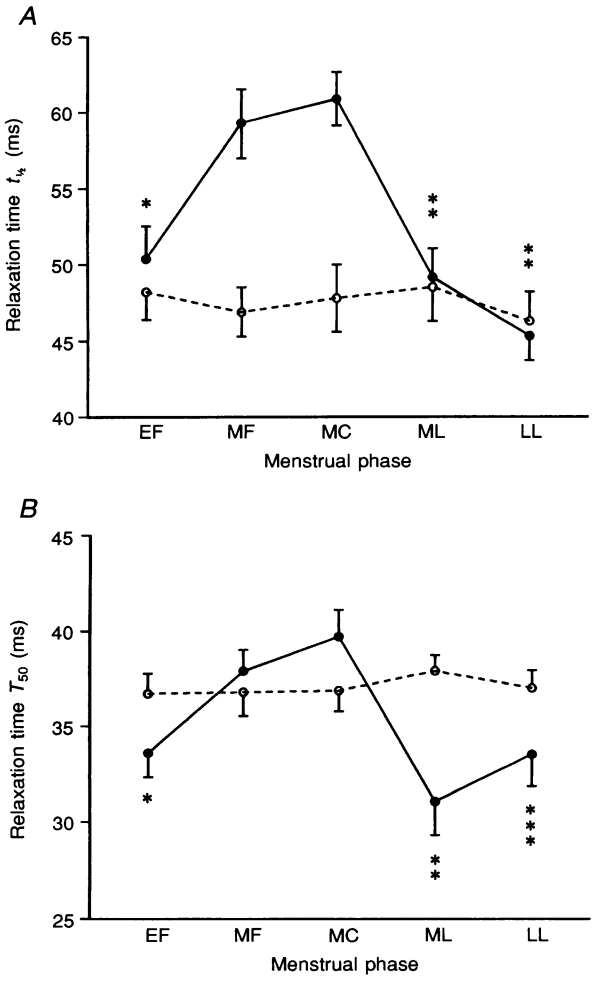

Figure 2. Relaxation times for the quadriceps from twitch and tetanus

Relaxation times from twitch ($t_{\frac{1}{2}}$; *A*) and from 50 Hz tetanus (T_{50}; *B*) in the non-pill (●) and OC (○) groups. Significant difference from MC: * $P < 0{\cdot}01$, ** $P < 0{\cdot}005$, *** $P < 0{\cdot}001$.

LL, $P < 0{\cdot}005$). No changes in the force–frequency relationship occurred in the women taking the OC.

Quadriceps fatigue index

The quadriceps muscle was more fatiguable at MC in the non-pill group compared with other phases of the cycle, with the difference being significant for the luteal phases (ML, $P < 0{\cdot}001$; LL, $P < 0{\cdot}005$). There were no differences in the fatigue index throughout the cycle in the OC group (Fig. 3).

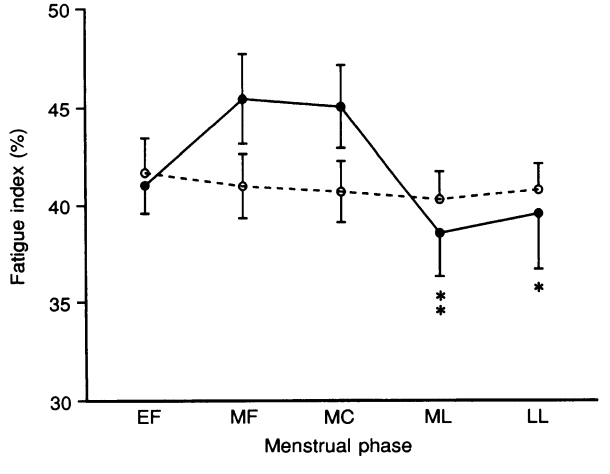

Figure 3. Quadriceps fatigue index during the different phases of the cycle

●, non-pill group; ○, OC group. Significant difference from MC: * $P < 0{\cdot}005$, ** $P < 0{\cdot}001$.

DISCUSSION

Significant changes in quadriceps and handgrip strength, quadriceps contractile properties and fatiguability have been found throughout the menstrual cycle of women not taking the OC. At mid-cycle (corresponding to the ovulatory phase) the muscle was stronger, slower and more fatiguable. These changes were not seen in women taking the OC. The strength results agree with those of Phillips *et al.* (1993*a*), although the variations in strength were not as great as in

their study when 20% changes in strength were found for the AP muscle between the ovulatory and luteal phases.

A number of hormonal changes take place around ovulation, including a rise in oestrogen, testosterone, luteinizing hormone and follicle stimulating hormone. Levels of oestrogen and progesterone are higher in the luteal phase of the cycle compared with the follicular phase. However, the highest oestrogen levels are seen just prior to ovulation. Phillips *et al.* (1993*a*) suggested that it is this surge in oestrogen which may be responsible for the increase in muscle strength found at this time. Very little is known about the effect of oestrogen on muscle, which is perhaps rather surprising considering the widespread involvement of women in high performance sports and the use of oestrogenic agents to enhance meat production in farm animals. Oestrogen receptors have been identified in rat (Dube, Lesage & Tremblay, 1976), bovine (Sauerwein & Mayer, 1989) and rabbit (Saartok, 1984) skeletal muscle. Their presence in human skeletal muscle remains unconfirmed.

Testosterone receptors are present in muscle and are thought to exert an anabolic effect (Florini, 1987). As testosterone levels are raised at ovulation, it is possible that the effects seen are due to testosterone. We have compared the contractile properties of young men with the results for women during the different cycle phases and found that the only differences occurred at mid-cycle (Beltran Niclos, Welsh, Sarwar & Rutherford, 1995). This might suggest that testosterone is not the hormone responsible for the cyclic changes in contractile properties.

If oestrogen is the hormone responsible for the changes measured then it might be expected that the greatest differences would be between the follicular and ovulatory phases, as oestrogen levels are relatively high during the luteal phase. In fact the greatest differences were found between the luteal and ovulatory phases. One possible explanation is that progesterone is inhibitory to the effects of oestrogen, as it is for many of its other actions especially on the reproductive system. Alternatively it may be that progesterone is having an effect on the muscle, causing it to be weaker in the luteal phase. However, the results on post-menopausal women, where the muscle is weak for its size, even when progesterone levels are low (Rutherford & Jones, 1992; Phillips *et al.* 1993*b*), suggest that this is not the case. The rapidity of the changes in strength strongly suggests that they could not be caused by changes in muscle size but may be due to changes in the force produced by the cross-bridges. Phillips *et al.* (1993*b*) found that the forces generated during a stretch were maintained at the times when isometric force was reduced during the menstrual cycle. This is analogous with the situation following the menopause when there is maintenance of the stretch force when force per unit CSA is reduced (Vandervoort, Kramer & Warren, 1990; Philips *et al.* 1993*b*). These results indicate that there is no decrease in the number of attached cross-bridges or level of activation as both would result in loss of stretch force. The work on human muscle resembles parallel studies on mouse muscle following ageing (Brooks & Faulkner, 1988; Phillips, Bruce & Woledge, 1991) and following oophorectomy (Phillips, Rowbury, Bruce & Woledge, 1993*c*). In each case a reduction in force per unit CSA was accompanied by maintenance of the stretch force. One explanation for these findings is that the force produced by each cross-bridge is reduced through a change in the equilibrium between the 'low' and 'high' force states of the cross-bridge. A switch between the two states and maintenance of the stretch force is known to occur when inorganic phosphate (P_i) levels are high (Pate & Cooke, 1989). The mechanism by which changing oestrogen levels could affect muscle P_i is unknown. Phillips, Wiseman, Woledge & Kushmerick (1993*d*) did not find altered P_i in muscles from ageing mice, but this has not been investigated in human muscle following the menopause or during the menstrual cycle.

This is the first study to show changes in muscle relaxation times during the cycle. The slowing of relaxation at mid-cycle resulted in a leftward shift in the force–frequency relationship. The relaxation times could be affected by the activity of the myosin ATPase or the re-uptake of calcium by the sarcoplasmic reticulum. Increases in P_i have been associated with a slowing of relaxation in human first dorsal interosseus muscle, as have decreases in pH (Cady, Elshove, Jones & Moll, 1989). As mentioned above, it is not known if fluctuations in P_i or pH occur during the menstrual cycle.

Temperature is also known to strongly influence relaxation rate, with increases in the rate accompanying temperature rises (Davies, Mecrow & White, 1982). It is unlikely that changes in muscle temperature during the cycle could explain our findings as the muscle was fastest during the LL and EF phases when basal body temperature would not be expected to be higher than during the MF and early MC phases.

Respiratory muscle fatigue has been shown to be lower during the luteal phase when compared with the follicular phase (Chen & Tang, 1989), similar to the results presented here for the quadriceps. There are a number of possible explanations for the changes in fatiguability. During the luteal phase the muscle may be warmer, coincident with the rise in basal body temperature brought about by progesterone. This, in turn, may increase the blood supply to the muscle which could reduce fatigue. Glycogen storage is also known to change during the cycle, with muscle and liver stores being greater during the luteal phase (Nicklas, Hackney & Sharp, 1989) under the influence of oestrogen and progesterone. In the fatigue protocol used in our study, the muscle would be expected to be ischaemic for much of the test and therefore reliant on muscle glycogen stores for energy. These, however, should not be limiting over such a short time scale.

No changes were seen in any parameter in the women taking the OC. For the 21 days of administration they were taking a constant oestrogen and progestin dose. Measurements were also made at variable times during the 7 days off the pill, but on average no changes were observed at this time. Ethinyl oestradiol levels remain elevated up to at least 24 h after ingestion and progestin levels for up to 4–5 days (Crosignani & Vecchia, 1994). Any changes in muscle function could therefore have been obscured by testing at variable times after the last pill was taken. More frequent testing is required to examine the effect of pill withdrawal on muscle parameters.

We have demonstrated changes in strength, relaxation and fatiguability in human muscle during the menstrual cycle which may be due to fluctuations in sex steroid levels, in particular oestrogen. Further work is required to confirm the link between strength increases and ovulation and to identify the hormone and mechanism responsible for the observed changes.

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